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Reliability of C-reactive protein as an inflammatory marker in patients with immune-mediated inflammatory diseases and liver dysfunction

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Abstract

Objectives: CRP is an acute-phase reactant widely used clinically as a marker of inflammation. CRP is a protein synthesized by hepatocytes. Previous studies have shown lower CRP levels in response to infections in patients with chronic liver disease. We hypothesized that CRP levels would also be lower during active immune-mediated inflammatory diseases (IMIDs) in patients with liver dysfunction.

Methods: This retrospective cohort study used Slicer Dicer in Epic, our electronic medical record system, to search for patients with IMIDs both with and without concomitant liver disease. Patients with liver disease were excluded if there was no clear documentation of liver disease staging. Patients were also excluded if a CRP level was not available during disease flare or active disease. Arbitrarily, we considered normal CRP as $\leq$0.7 mg/dl, mild elevation of CRP as $\geq$0.8 and <3mg/dl, and elevated CRP as $\geq$3mg/dl.

Results: We identified 68 patients with both liver disease and IMIDs (RA, PsA and PMR) and 296 patients with autoimmune disease and without liver disease. Presence of liver disease had the lowest odds ratio (odds ratio = 0.25, $P < 0.0001$) of having an elevated CRP during flare. Each specific IMID, except SLE and IBD, had higher median CRP levels during active disease episodes in patients without liver disease than in those with liver disease.

Discussion: Overall, IMID patients with liver disease had lower serum CRP levels during active disease than their counterparts without liver dysfunction. This observation has implications for clinical use of CRP level as a reliable marker of disease activity in patients with IMIDs and liver dysfunction.

Lay Summary

What does this mean for patients?
This study evaluated charts of patients with and without liver disease who had immune-mediated inflammatory diseases. We looked at the inflammatory protein C-reactive protein (CRP), which is made by the liver and which can be used to measure inflammation and disease activity in immune-mediated inflammatory diseases. We compared CRP levels during disease flares of different diseases in patients with and without liver disease. Overall, median CRP levels were lower in patients with liver disease. This shows that, in patients with liver disease, CRP levels might not be as reliable a marker for inflammation and disease flare as it is in patients without liver disease.

Keywords: CRP, inflammatory markers, liver disease, disease activity, autoimmune disease, immune-mediated inflammatory disease

Key messages

- CRP levels are lower in active immune-mediated inflammatory diseases in patients with liver disease than those without liver disease.
- CRP level increases less during disease flares in RA, PsA and PMR in patients with liver disease than in those without liver disease.
- Liver disease stage does not influence degree of CRP elevation.

Introduction

CRP is an acute-phase reactant that is widely used as a marker of inflammation [1–5]. Serum CRP levels can be elevated with any type of inflammation, including immune-mediated inflammatory diseases (IMIDs) and infections [1–3]. IMIDs are defined as conditions in which dysregulation of the immune system leads to organ system dysfunction [6]. The median CRP level in normal, healthy subjects is ~0.8 mg/l [1, 2, 4]. Many different things influence the baseline CRP level, including age, sex and weight [1].

CRP is a protein synthesized by hepatocytes in response to inflammation [1, 3–5, 7]. Inflammation causes a rapid

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increase in CRP levels, which are often used clinically as reliable measures of disease activity and response to treatment in RA [2, 3, 5]. CRP is not as consistently elevated in clinically active PsA but is a good prognostic indicator in PsA and one of the only existing biomarkers to evaluate disease activity [8]. In PMR, CRP is a more sensitive indicator than ESR of disease relapse or flare [9]. In SLE, CRP is generally elevated only during active arthritis or acute serositis but, interestingly, not in other active disease manifestations, and therefore, is seldom relied upon as a marker of flare [3, 10]. In IBD, elevated CRP levels have been closely correlated with inflammation on endoscopy [4]. In many IMIDs, CRP is the best or only way to assess the state of disease activity. Because of this, it is imperative to ensure that CRP measurements are accurate.

Previous studies in patients with infections have shown lower than expected CRP levels in those with liver disease [5]. Given that CRP is produced by hepatocytes, we hypothesized that liver disease might lead to curtailed increases in CRP levels in patients with IMIDs. The aim of this study was to determine whether CRP is a dependable measure of IMID activity in patients with liver disease.

Methods

This retrospective cohort study used Slicer Dicer in Epic, the electronic health-care record used by MetroHealth Medical Center, to search for patients with IMIDs both with and without concomitant liver disease. To ensure that sufficient patients were included in this study, the search dates for patients with liver disease were between 1 January 2010 and 15 August 2020. For patients with IMIDs and without liver disease, search dates were between 1 January 2019 and 15 August 2020. This study was approved by the MetroHealth Medical Center Institutional Review Board.

To identify patients with IMIDs, we searched in Slicer Dicer for individual disease ICD-10 codes for RA, PMR, PsA, unspecified inflammatory arthritis, SLE, IBD (and individual searches for Crohn's disease and ulcerative colitis) and others. We also searched for at least one visit in the department responsible for diagnosis of these conditions and reviewed all patient charts to ensure that diagnoses were accurate.

Liver disease search criteria included ICD-10 codes for chronic liver diseases with at least one gastroenterology visit. Charts were reviewed to determine the accuracy of search criteria and the cause and staging of liver disease. Patients with liver disease were included only if there was clear staging of their liver disease via the model for end-stage liver disease (MELD) score, Child-Pugh score, fibroscan, fibrosure or liver biopsy. Based on these staging methods, liver disease was classified as mild, moderate, severe, or very severe. Mild liver disease included MELD $\leq$10, Child-Pugh A (5 or 6), and fibrosis scores of F0–F1. Moderate liver disease included MELD 11–18, Child-Pugh B (7–9) and fibrosis score of F2. Severe liver disease included MELD 19–24, Child-Pugh C (10–15) and fibrosis scores of F3–F4. Very severe liver disease included patients with MELD $\geq$25. We used the most severe liver disease stage listed in each patient chart.

Patients were excluded if the CRP level was not checked during disease flare or active disease. Flare or active disease was determined by provider documentation in Epic. We arbitrarily considered normal CRP as $\leq$0.7 mg/dl, mild elevation of CRP as $\geq$0.8 mg/dl and <3mg/dl, and elevated CRP as $\geq$3mg/dl.

Statistical analysis of variable influence on median CRP levels was performed using ordinal linear regression. Statistical significance was considered $P < 0.05$.

Results

We identified 68 patients with liver and autoimmune disease and 296 patients with autoimmune disease and no liver disease (Table 1). Most patients in both groups were female, but the group without liver disease had a higher percentage of women than the group with liver disease (80.1% *vs* 57.4%, respectively). The mean age of both groups fell in the middle age range, but the group with liver disease was somewhat older. Mean BMI for both groups was obese, but marginally higher in those without liver disease.

IL-6 inhibitors are used to treat some IMIDs and are known to reduce serum CRP levels [11]. There was one patient with liver disease and 12 without liver disease who were treated with an IL-6 inhibitor (Table 1). Each patient taking an IL-6 inhibitor had at least one CRP value while they were not on the medication, hence this variable did not have significant bearing on study outcomes and analysis was therefore not performed on this variable.

RA and PsA were the most common IMIDs in both groups of patients. SLE and IBD were the next most prevalent diseases. Across all IMIDs, the median CRP (mg/l) during active disease was higher in those without liver disease than in those with liver disease (1.3 *vs* 0.8, respectively). This trend was also true for each specific IMID apart from SLE and IBD (Fig. 1). Median CRP (mg/l) was higher in RA patients with no liver dysfunction than in those with liver dysfunction (1.35 *vs* 0.88, respectively). PsA patients without liver disease had a higher median CRP (mg/l) than those with liver disease (1.1 *vs* 0.65, respectively). Median CRP (mg/l) was higher in PMR patients without liver disease compared with those with liver disease (1.45 *vs* 0.7, respectively). The stage of liver disease did not have a significant impact on median CRP during flare (Fig. 2). The presence of liver disease had the lowest odds ratio (odds ratio = 0.25, $P < 0.0001$) of having an elevated CRP

Table 1. Patient demographics

Characteristic	Liver disease ($n = 68$)	No liver disease ($n = 296$)
Female, *n* (%)	39 (57.4)	237 (80.1)
Male, *n* (%)	29 (42.6)	59 (19.9)
Age, mean (S.D.), years	62.9 (11.9)	56.9 (14)
BMI, mean (S.D.), kg/m^2	30.9 (6.8)	32.2 (8.8)
CRP, median, mg/dl		
Active disease	0.8	1.3
Non-active disease	0.5	0.6
Infection	4.2	12.4
IMID		
RA	24	204
PsA	14	47
SLE	2	23
IBD	10	24
PMR	6	5
Inflammatory arthritis	3	4
Other	14	14
IL-6 inhibitor	1	12

IMID: immune-mediated inflammatory disease.

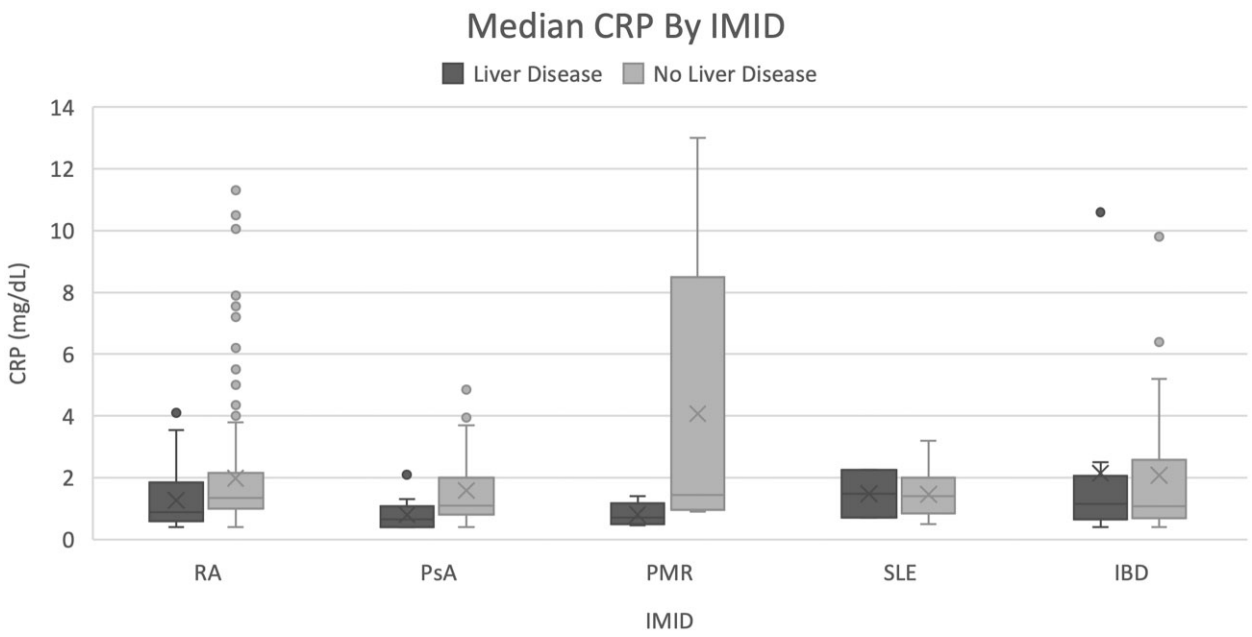

Figure 1. Flare CRP by autoimmune disease with and without liver disease

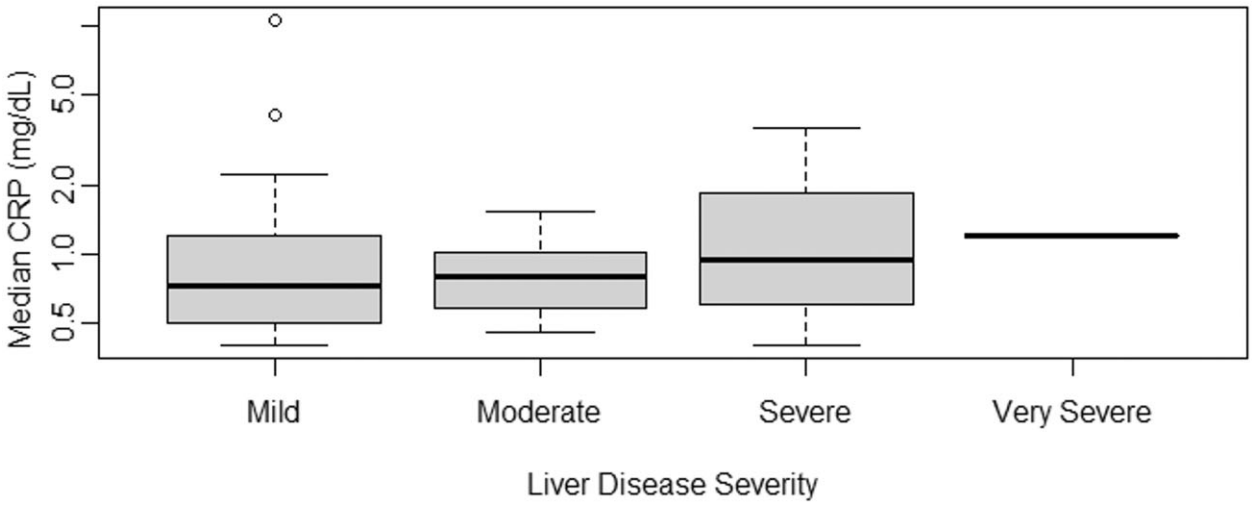

Figure 2. Median flare CRP by liver disease severity

Table 2. Odds ratio via ordinal linear regression of independent variable association with elevated CRP during disease flare

Variable	Odds ratio (95% CI)	*P*-value
Liver disease	0.25 (0.14, 0.43)	<0.0001
Overweight BMI	1.94 (1.05, 3.61)	0.036
Obese BMI	2.04 (1.19, 3.51)	0.009
Age	1.01 (0.99, 1.03)	0.201

during disease flare in comparison to other factors, and this was statistically significant (Table 2).

Discussion

Patients with liver disease had lower median serum CRP levels during active IMID states than their counterparts without liver dysfunction. This was true for most of the individual IMIDs studied, excluding SLE and IBD. Given that CRP levels might not be reflective of active disease in SLE, this was not unexpected [3, 10]. Faecal calprotectin levels have shown a much closer association with active inflammation than CRP levels in IBD, which might also explain the discrepancy in the pattern of CRP levels in this disease [12]. In some IMIDs, however, CRP is the most trusted way of monitoring disease activity [2–5, 8, 9]. Given that CRP is one of the few markers of disease flare in many IMIDs, it is important to recognize factors that might influence this measurement. Age and weight, among other things, are known to affect CRP levels [1]. It now appears that liver disease should be added to the list of entities that can impact CRP levels. Although liver disease can affect CRP levels, the severity of liver disease does not seem to determine the size of the effect.

Some variability in inflammatory marker levels in our study might be related to documentation. If a provider note did not contain any documentation of disease activity associated with collected inflammatory markers there was no way to discern

disease activity, and those inflammatory markers were therefore not analysed. Also, there was variability in the severity of disease activity. Whether disease was documented as minimally or extremely active, it was considered a flare for the purposes of this study. The retrospective nature of this study did not allow for standardization of disease activity measures, hence clinical quantification of disease activity should be considered for investigation in future studies.

This study was somewhat limited by the number of patients available. Given that staging was not documented in the chart of every patient with liver disease, the number of available patients with concomitant liver disease and IMID was decreased. Also, many patients were eliminated from evaluation if they did not have a CRP level measured during active disease, which reduced the number of patients assessed. Future studies with larger numbers of patients would be helpful to substantiate the findings of this study.

The fact that CRP values can be influenced by so many variables emphasizes the importance of checking this inflammatory marker frequently to establish patterns for individual patients. The presence of liver disease seems overall to lower CRP levels, although an association of such levels with disease activity in these patients may still be evident. Despite the overall decrease in CRP values, there is likely still to be a pattern that can be established by following CRP trends over time.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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